REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. Claim Status and Amendments

Claims 16-32 were pending in this application when last examined. Claims 27 and 28 were withdrawn as non-elected subject matter. Claims 16-26, and 29-32 were examined on the merits and stand rejected.

Claims 16-32 have been cancelled without prejudice or disclaimer thereto and replaced with new claims 33-52. It is noted that the present amendment has cancelled the withdrawn claims without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any cancelled subject matter.

Support for new claims 33-52 can be found throughout the disclosure in general and previous claims 16-32. No new matter has been added.

Claims 33-52 are pending after this amendment.

II. Objection to the Declaration

The Official Action objected to the declaration on the basis that it contains non-initialed and/or non-dated alterations. See item 4 on page 2.

Attached herewith is a revised declaration that has been newly executed by all inventors. The attached declaration does not contain non-initialed and/or non-dated alterations. Accordingly, the attached declaration renders the objection moot. Withdrawal of the objection is requested.

III. Claim Objections

Claims 18-21 were objected for being improper dependent claims for allegedly failing to further limit the subject matter of previous claim. See item 5 on pages 2-3 of the Official Action.

Claims 29-32 were objected for depending on a non-elected claim. See item 6 on page 3. The present

Claims 23 and 29-32 were objected to for the recitation "sequence SEQ ID NO: 2" and "protein SEQ ID NO: 2" on the basis that such are grammatically not correct. See item 7 on page 3 of the Official Action.

It is believed that the present amendment overcomes the objections for reasons which are self-evident. In particular, the amendment replaces the objected claims with new claims 33-54 that do not contain the objected language. The new claims contain language suggested by the Official Action. Withdrawal of the objections is solicited.

IV. Non-Statutory Subject Matter Rejection

Claims 16, 17, and 18 were rejected under 35 U.S.C. § 101, as being non-statutory subject matter for the reasons in item 8 on pages 3-4 of the Official Action.

The present amendment overcomes this rejection by replacing the rejected claims with new claims 33-36. The new claims recite "An isolated protein" or "An isolated nucleotide sequence" as suggested in the Official Action. Thus, withdrawal of the rejection is solicited.

V. Indefiniteness Rejection

Claims 16-22, 24-26, and 29-32 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons in items 10-19 on pages 4-6 of the Official Action.

It is believed that the present amendment overcomes the objections for reasons which are self-evident.

It should be noted that Applicants have drafted the new claims along the lines suggested by the Official Action, for instance, in items 11 and 13. Applicants have also drafted the new claims to remove the objected language in items 12 and 15. In reply to item 14, new claims 43 and 45 define the "paraoxonase" protein by reference to SEQ ID NO.

As to the concerns regarding old claims 29-32 in items 16-18, Applicants have drafted new method claims 48-54 to positively recite method steps as suggested by the Official

Action. In doing so, old claim 26 has been replaced new claim 48 that discloses a method for determining the concentration of a protein of SEQ ID No: 1.

Regarding the antibodies, it is now specified in the third step that an antibody marked with peroxidase and raised against the antibody fixed in the plate is used.

Also, as mentioned in the specification, this method corresponds to an ELISA method. The terms "peroxidase fixed in the plate" have been suppressed and replaced by "peroxidase" only. Regarding the substrate of peroxidase, as mentioned in the specification, said substrate is commercially available in a kit provided by Sigma. Moreover, at the filing date, it was known that peroxidase substrate is H_2O_2 (see for example Veitch et al., Phyotochemistry, 65 (2004): pp. 249-259; copy enclosed herewith).

New claim 48 discloses that the reaction is stopped by TMB addition.

Further, at the filing date, the skilled person knew that peroxidase from horseradish (HRP) is commonly used in association with a luminol derivative, in presence of H_2O_2. The reaction with luminol generates photons, which is proportional to the quantity of HRP. Photons are detected by a luminometer. The reaction is stopped by addition of TMB. Indeed, the added TMB captures O_2 produced by the previous reaction and becomes

oxidized. In the oxidized form, TMB has an emission wavelength that can be detectable at 450 nm, with a spectrophotometer.

Thus, based on the teachings in the disclosure and the knowledge in the field, a person with ordinary skill would be able to reproduce exactly the peroxidase reaction such as claimed in new claim 48. New claim 48 takes its support in the specifications page 5, lines 4-26.

As to the concern regarding old claims 29-32, it should be noted that the new claims further specify the conditions corresponding to an *in vitro* diagnosis of a disease linked to hyperphosphataemia (when the concentration of the isolated protein of SEQ ID NO: 2 or SEQ ID NO: 3 as assayed is less than the quantity of the protein normally present in the blood of a healthy individual) (new claim 50) and hypophosphataemia (when the concentration of the protein of SEQ ID NO: 2 or SEQ ID NO: 3 as assayed is greater than the quantity of the protein normally present in the blood of a healthy individual) (claim 51).

In this regard, it is well established that definiteness of claim language is analyzed, not in a vacuum, but in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). See

also, M.P.E.P., Eighth Ed., Rev. 6 (September 2007) at § 2173.02.

The specification describes the clinical or physiological conditions associated with hyperphosphataemia and hypophosphataemia. See, for instance, the discussion at page 1, lines 9-26 and page 6, lines 1-32. The terms hyper- or hypo- phosphataemia correspond, as mentioned in the specification page 1 and page 4 for example, to an excess or reduced concentration of phosphate in an organism, in particular in plasma.

For example, as mentioned in page 1 of the specification, increase of plasmatic phosphate (hyperphosphataemia) is associated with high risk to develop cardiovascular diseases, said high concentration of phosphate promoting the processes of atherosclerosis and calcification of the arteries.

At the filing date, the skilled artisan would know what pathologies are associated with hyper- or hypo-phosphataemia, in particular from the teaching of Weisinger J. et al., The Lancet, 1998, Volume 352, Issue 9125, pp. 391-396 (enclosed herewith).

Regarding atheroma plaque definition, any skilled in the art who has some medicine knowledge would know the definition of atheroma. This definition was known at the filing date. For instance, a definition of atheroma is

Atherosclerosis/atheroma, which is the clogging or hardening of arteries or blood vessels caused by plaques (accumulations of fatty deposits, usually cholesterol). See for instance, the Definition found in http://wwwjuliantruhin.com/dictionaiy/medicine/atheroscierosi.html).

Thus, at the filing date, it is believed that skilled artisan would clearly understand which pathologies are linked to phosphorus dysfunction, and in particular atherosclerosis.

In view of the above, the claims are thus believed to be clear, definite and have full antecedent basis.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

VI. Enablement and Written Description Rejections

Claims 24, 25, and 29-32 were rejected under 35 U.S.C. § 112 on the basis the specification lacks an enabling disclosure for diagnosis and pharmaceuticals/therapeutics for the reasons set forth in items 21-23 on pages 7-10.

Claims 16-22 and 24-25 were rejected under 35 U.S.C. § 112 on the basis the specification lacks written description support for the "variants" language in the claims for the reasons stated in item 24 on pages 10-13 of the Official Action.

These rejections are respectfully traversed as applied to the amended claims.

As to the method of diagnosis, the Official Action contends that the present application does not provide any guidance for the claimed method of diagnosis, *i.e.*, the specification does not give information about the biological role of HPBP proteins in the claimed pathologies.

As acknowledged in the Official Action, HPBP proteins are novel, and thus the prior art is free of information about these proteins.

Nonetheless, Applicants have unexpectedly found that these new proteins HPBP are able to interact with a well known protein: paraoxonase protein (PON1). The following Figure 1 represents the binding assay between PONI and HPBP. The two proteins have a very high affinity to each other (5 nM).

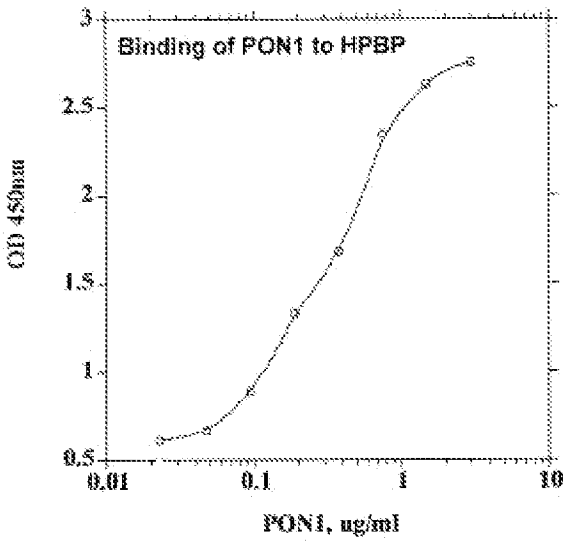

Figure 1

PON1 is present in plasma in association with High Density Lipoproteins (HDL).

The following Figure 2 represents the binding assay between PON1 and HDL. PON1 has a very high affinity to HDL (5 nM), similar to its affinity to HPBP.

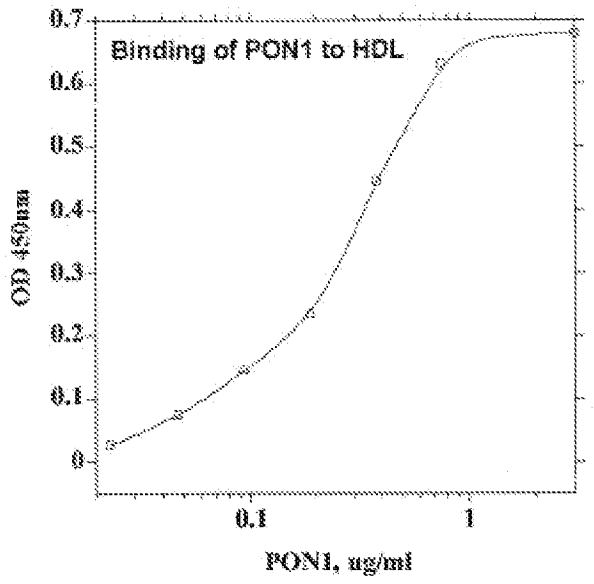

Figure 2

In addition, Applicants have demonstrated that HPBP does not interact with HDL.

The following Figure 3 represents the binding assay between HPBP and HDL. As shown in the figure, HPBP is not able to associate with HDL.

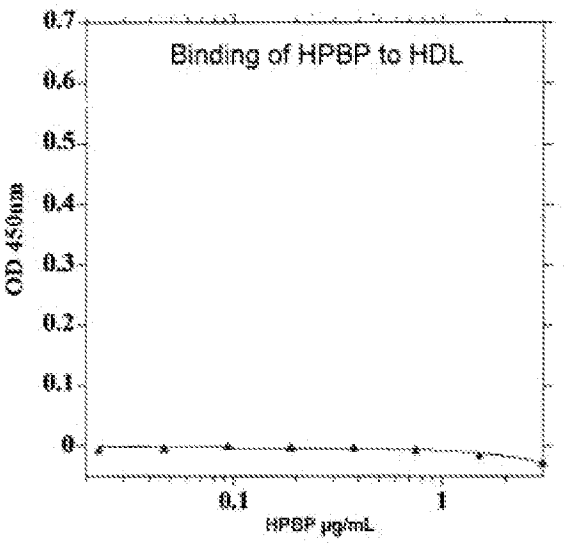

Figure 3

In view of these results, it is easy to understand that HPBP could interfere with the interaction between PON1 and HDL.

Thus, if HPBP concentration is higher than the concentration of HDL, PON1 would preferably interact with HPBP. Inversely, if HPBP concentration is lower than the concentration of HDL, PON1 would preferably interact with HDL.

PON1 has a positive toxicological role, protecting from environmental poisoning by organophosphate derivative. The role of PON1 associated with HDL has been clearly established against risk to develop atherosclerosis as evidenced by the attached copies of Mackness et al. (Journal of Arteriosclerosis, Thrombosis, and Vascular Biology, 21: 473-480 (2001)) and Shih et al. (Nature, vol. 394, pp. 284-287, 1998).

Thus, regarding the competition between PON1 for its interaction with HPBP or HDL, concentration of HPBP would modulate the protective effect of PON1-HDL.

Therefore, the concentration of HPBP in plasma would indicate the risk, in a patient, to develop atherosclerosis.

As a consequence, at the filing date, it is respectfully submitted that the Applicants were in possession of the claimed invention and knew that evaluation of HPBP concentration would be important to diagnose pathologies associated with modulation of inorganic phosphorus. Thus, it is respectfully submitted that the skilled artisan could practice the claimed method without undue experimentation using the guidance in the disclosure and the knowledge in the art.

Lastly, as to the written description rejection, it should be noted that the new claims do not contain the objected "variants" language of the old claims.

For these reasons, the enablement and written description rejections are untenable and should be withdrawn.

VII. Double Patenting Rejection

Claim 25 was provisionally objected under 35 C.F.R. § 1.75 as being a substantial duplicate of claim 24 for the reasons in item 26 on page 13 of the Official Action.

It is believed that the present amendment overcomes this rejection by replacing the rejected claim with new claim 45 that has been drafted to obviate this concern. Withdrawal of the rejection is solicited.

VIII. Conclusion

Having addressed all of the issues in the Office Action, the present application is in condition for allowance and early notice to that effect is hereby requested. If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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JFW/ml

APPENDIX:

The Appendix includes the following item(s):

- Declaration;
- Veitch et al., Phyotochemistry, 65 (2004): pp. 249-259;--
- Weisinger J. et al., The Lancet, 1998, Volume 352, issue 9125, pp. 391-396;
- Mackness et al., Journal of Arteriosclerosis, Thrombosis, and Vascular Biology, 21: 473-480 (2001);
- Shih et al., Nature, vol. 394, pp. 284-287, 1998.